building a relational database of protein structural variants based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:

3-D molecular coordinates for structural variant-drug complex models; and

observed clinical data associated with the genetic polymorphisms;

obtaining a target protein structural variant encoded by a gene exhibiting genetic polymorphism in a patient;

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generating a 3-D protein model based on the patient's gene sequence;

screening or comparing the 3-D model derived from the patient to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the patient; and

predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

REMARKS

A check in the amount of $645.00, which includes $465.00 for a three month extension of time (37 CFR §1.17(a)(3) Small Entity Fee) and $180 for a Supplemental Information Disclosure Statement is enclosed. Any fees, including fees for additional claims and an extension of time, that may be due with this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for Extension of Time is required, this paper is to be considered such Petition.

Claims 23 and 41-49 are pending in the application. Claim 23 is amended to particularly point out and distinctly claim that which applicant regards as the invention. In particular, the phrase "a molecular graphics interface for 3-D molecular structure visualization; functionality for protein sequence and structural analysis; database searching tools;" is deleted, and the deleted subject matter is claimed in new claim 41 as noted below. Basis for amendment

of claim 23 can be found, for example, at page 6, lines 27-20, at page 16, lines 25-30, and at page 18, lines 11-26, which describe databases with clinical data and 3-D molecular structure data.

In addition, the words "derived" and "the" are deleted for grammatical clarity. The phrase "based on the same" is replaced with the phrase —encoded by a— and the phrase "associated with a polymorphism" is replaced with the phrase —exhibiting genetic polymorphism— for grammatical clarity. This amendment finds basis in claim 23 as originally filed and at page 31, line 24, of the specification which states that the structural variants are encoded by genes. The word "subject" is replaced with the word "patient" for clarity and finds antecedent basis in claim 23 which recites the word "patient." The phrase "screening/comparing" is replaced with the phrase —screening or comparing— for grammatical clarity. The amendment finds basis at page 5, lines 15-30, of the specification which describes that a patient structural variant model is screened against references models in one embodiment and compared to reference models in another embodiment. No new matter has been added.

New dependent claim 41 captures subject matter deleted from claim 23 by the instant amendment by stating that the method of claim 23 further includes the steps of providing the database with a molecular graphics interface that interfaces with the database for 3-D molecular structure visualization; providing the database with functionality that interfaces with the database for protein sequence and structural analysis; and providing the database with searching tools that interface with the database. Thus, claim 41 finds particular basis in original claim 23 (see, also, page 17, lines 1-28 and page 18, line 27 to page 19, line 5, of the specification, which states that the database is interfaced with molecular graphics, search tools, and tools for analyzing protein sequence and structure. Claims 42-44 and 46-48 find basis particular basis, for example, at page 12, line 20, to page 16, line 24, of the specification which describe ways of generating 3-D protein structures. Claims 45 and 49 find basis, for

example, at page 5, lines 17-26; at page 6, lines 27-30; at page 16, lines 25-30; and at page 17, line 14 to page 18, line 29, which describe that reference protein structural variant models and data for molecular structures of these models are stored in the databases. No new matter has been added.

Pursuant to 37 C.F.R. § 1.121, a marked-up version of amended claim 23 is included as an attachment.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

A Supplemental Information Disclosure Statement and Form PTO-1449 (1 page) making of record art cited in the Response accompanies this response.

THE REJECTION OF CLAIM 23 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claim 23 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most clearly connected, to make and/or use the claimed subject matter. Specifically, the the Office Action states that generating 3-D protein structural variant models from the sequences would require undue experimentation because (a) there would be an unpredictable amount of experimentation required to determine the structure of a polypeptide from a polymorphic site by use of sequence data, (b) the specification does not present specific guidance to determine the structure of a polypeptide from sequence data, (c) the specification does not provide a working model of determination of the structure of a polypeptide from sequence data, (d) the nature of the claimed subject matter is complex, (e) the state of the art as represented by Sternberg *et al.* and Koehl *et al.* indicate that *ab initio* methods are unable to predict accurately, structures of complete polypeptides in the absence of knowledge of structures of polypeptides with similarity to the polypeptide of interest, (f) the skill of those in the art of polypeptide structure modeling is high, (g) Sternberg *et al.* and Koehl *et al.* indicate that *ab initio* methods of structure prediction from polypeptide sequence information alone is not predicted to result in accurate structure of a complete polypeptide, and (h)

the claims are broad in that they are drawn to modeling molecular structures in the absence of information other than sequence information. This rejection is respectfully traversed with respect to claim 23 and insofar as it applies to any of claims 41-49.

RELEVANT LAW

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of 35 U.S.C. §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require **undue** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

Analysis

Applying the above factors to the instant claims, applicant respectfully submits that as described in detail below, it would not require undue experimentation to practice the claimed methods.

1. Breadth of the claims

23. (Amended) A computer-based method for predicting clinical responses in patients based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences for a target protein that is the product of a gene exhibiting genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

building a relational database of protein structural variants based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:

3-D molecular coordinates for structural variant-drug complex models; and

observed clinical data associated with the genetic polymorphisms;

obtaining a target protein structural variant encoded by the gene exhibiting genetic polymorphism in a patient;

generating a 3-D protein model based on the patient's gene sequence;

screening or comparing the 3-D model derived from the patient to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the patient; and

predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

Hence the claim is directed to computer-based methods for predicting clinical responses in a patient in which models of structural variant proteins in patients are generated and compared to structural variant models in a database. Clinical data associated with structural variant models that are similar to the patient's structural variant models are used to predict clinical outcomes for the patient.

Dependent claim 41 further describes the database as being interfaced with molecular graphics for visualization, with searching tools, and with

functionality for analyzing protein sequence and structure, which aid in the comparison of the patient's structural variant model with the structural variant models in the database.

Dependent claims 42-44 and 46-48 further describe ways of generating the 3-D protein structure models that are in the database or that are obtained from patients. Such methods include experimental methods, protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, and/or *ab initio* methods. Claims 45 and 49 further describe the database as comprising 3-D molecular structrual data of the structural variant models.

2. The amount of direction and guidance presented, teachings of the specification

Each step of the process is taught in the instant specification. For example, the specification teaches how to obtain one or more amino acid sequences for a target protein that is the product of a gene exhibiting genetic polymorphisms (See e.g. page 12, line 21, to page 13, line 2). The specification further teaches that genes exhibiting polymorphisms can be obtained, for example, from patients or from publicly available databases and teaches that the amino acid sequences of the protein product of the genes exhibiting polymorphisms can be determined by, for example, sequencing methods (See e.g. page 12, line 21, to page 13, line 2).

The specification also teaches how to build a relational database of protein structural variants and of observed clinical data associated with the genetic polymorphisms, wherein the database contains 3-D molecular coordinates for structural variant-drug complex models and observed clinical data associated with the genetic polymorphisms (See e.g. page 16, line 25, to page 19, line 30, of the specification). The specification further teaches how to provide the database with a molecular graphics interface for 3-D molecular structure visualization, with tools for protein sequence and structural analysis,

and with searching tools (See e.g. page 17, lines 1-28 and page 18, line 27, to page 19, line 5 of the specification).

The specification teaches screening or comparison of the 3-D model derived from the patient to the structures contained in the database by identifying structures in the database that are similar to the model derived from the patient and predicting a clinical outcome for the patient based on the clinical data associated with the identified structures (See e.g. page 3, lines 4-5, page 5, lines 15-29, and page 20 lines 17-21 of the specification).

3-D protein structure generation

The specification provides a variety of methods for generating 3-D protein structural variant models from an amino acid sequence

The specification teaches a variety of ways to generate 3-D protein structural variant models from protein sequences (See e.g. page 12, line 20, to page 16, line 24). The step of "generating the structural variant models from protein sequences" in claim 23 includes any method by which such model can be constructed. For example, the specification teaches that 3-D protein structural variant models can be generated from "experimental methods, for example, x-ray crystallography or NMR, from a protein structure database, such as the PDB, or by using any of a number of well known techniques for predicting protein structure from sequence, for example, homology modeling, *de novo* protein folding algorithms and methodologies, and other computational protein structure prediction methods" (page 13, lines 3-11).

X-ray crystallographic data and molecular modeling

The specification provides working examples of how to determine protein structure from sequence data using x-ray crystallographic data and molecular modeling. In Example 1, the structure of NS3-peptide complexes is determined using sequence data in conjunction with crystallographic data of NS3/NS4A peptides and molecular modeling using Monte Carlo simulations and ECEPP/3 force field. Therefore, the specification teaches a skilled artisan how to use

protein sequence data to generate 3-D protein structure via x-ray crystallographic data and molecular modeling.

Homology Modeling

The specification teaches that one of skill in the art can generate 3-D protein structural variant models from the sequence of proteins by, for example, homology modeling in which proteins of unknown structure can be constructed using composite parts of related proteins with known structures (i.e. reference proteins; page 13, lines 16-21). The non-conserved regions of the protein of unknown structure can be constructed using, for example, database searching to identify other proteins with similar variable regions (page 14, lines 26-29). Sequence homology studies can be carried out using sequence alignment algorithms well known in the art (page 14, lines 6-7 and page 15, lines 5-7). Homology modeling can be used in conjunction with *ab initio* loop prediction or *ab initio* secondary structure prediction methods (Figures 2-3 and page 16, lines 3-24 of the specification) or conjunction with the *ab initio* methods described below to generate 3-D protein structures from sequence data. Therefore, the specification teaches a skilled artisan how to use protein sequence data to generate 3-D protein structure via homology modeling.

***Ab Initio* Methods**

Furthermore, contrary to statements in the Office Action, *ab initio* methods can be used to generate 3-D protein structures from sequence data; and such methods were known before the effective filing date of the application. For example, the specification teaches that *ab initio* methods, such as those taught in U.S. Patent Nos. 5,331,573; 5,579,250; and 5,612,895, cited on page 15, lines 8-13, of the instant application and incorporated by reference into the instant application can be used to generate 3-D protein structures from sequence data. The specification teaches that these methods involve simulating a real-size primary structure of a polypeptide in a solvent box, i.e., an aqueous environment; shrinking the size of the peptide isobarically and

isothermally; and expanding the peptide to its real size in selected time periods, while measuring the energy state and coordinates, i.e., the bonds, angles and torsions of the expanding molecule (page 15, lines 13-18). The specification teaches that as the peptide expands to its full size, it assumes a stable tertiary structure and that, in most cases, this tertiary structure will be either the most probable structure (i.e., it will represent a global minimum for the structure) or one of the most probable structures (page 15, lines 18-22). The specification also teaches that once a model it built, it can be refined using energy minimization or molecular dynamics calculations (page 15, line 26, to page 16, line 2).

These methods for *ab initio* generation of 3-D structures from sequence date are disclosed and claimed in the above-noted patents. U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895 each to Balaji *et al.* describe and claim methods of rational drug design that include simulating polypeptides in a way that predicts the most probable secondary and/or tertiary structures of polypeptides without any presumptions as to the conformation of the underlying primary or secondary structure.

In particular, the Balaji *et al. ab initio* methods include the steps of (a) simulating a real-size primary structure of a polypeptide of interest in a solvent box (e.g., in an aqueous environment); (b) shrinking the size of the peptide isobarically and isothermally; and (c) expanding the peptide to and beyond its real size in selected time periods, while measuring the energy state and coordinates, e.g., the ϕ, ψ angles, of the expanding molecule(s). As the peptide expands to its full size and beyond, it assumes a stable tertiary structure that is the most probable structure or one of the most probable structures. The Balaji et al methods can be practiced using three protocols. In one protocol, the residues of the peptide chain are shrunk and then expanded one at a time. In a second protocol, the entire peptide chain is shrunk and expanded simultaneously. In a third protocol, known physical and/or chemical data, if

any, can be used to bias the simulation towards a known result. Repetition of the *ab initio* technique and/or further analysis of the tertiary structure thus obtained, by using conformational energy plots, contour probability maps, and/or the Balaji plots disclosed in Balaji et al, provides a further measure of the probability of occurrence of the structure.

The Balaji plots used to analyze protein structure conformations can be generated from data gathered while performing the *ab initio* calculations or can be obtained from other sources. This data include the ϕ, ψ angles for each residue of the peptide as it expands to and beyond its normal size. The Balaji plot is used for: (a) identifying the relative proportional residence time adopted by a particular tertiary structure of a simulated peptide or peptidomimetic; (b) determining sequences or areas of flexibility and rigidness in such peptides or peptidomimetics; and (c) providing instructions and/or insight into the manner in which rigid, constrained or flexible peptide analogs should be modeled, e.g., by computer generation.

Once the most probable conformation of the polypeptide of interest is selected, analogs are designed and synthesized and evaluated for bioactivity. Additionally, peptidomimetics based on the conformation of the synthesized analogs are designed. Thus, the 3-D protein models generated by the Balaji *et al. ab initio* methods are useful in drug design methods.

In fact, the Balaji *et al. ab initio* methods were successfully used to predict the 3-D structures of endothelin-1 and to design bioactive analogs thereof (U.S. Patent No. 5,736,509). In particular, the drug design methods include the steps of (a) simulating the most probable conformations of endothelin-1 and selecting the most probable conformation from among the simulated conformations; (b) designing and synthesizing cyclic peptides that mimic selected surface features of the three-dimensional structure of endothelin-1; and (c) evaluating the bioactivity of the cyclic peptides (U.S. Patent No. 5,736,509). The cyclic peptides disclosed in U.S. Patent No.

5,736,509 mimic the surface of endothelin-1 and act as **antagonists and otherwise modulate the activity of endothelin**. Thus, the Balaji *ab initio* methods ar adequate for generating 3-D polypeptide structures for the design of bioactive molecules and drug analogs. The Examiner has provided no reasons why the Balaji *ab initio* methods cannot be used to generate 3-D structures of variant models for use in the instantly claimed methods of predicting clinical responses described in the instant application.

Combination of Homology Modeling and *ab initio* methods

The specification also teaches that a combination of homology modeling and *ab initio* methods can be used to generate structural variant models (page 16, lines 3-24). In particular, protein sequence information that is derived based on the genetic polymorphisms is used to assign the protein to a protein superfamily in order to identify related proteins to be used as templates to construct a 3-D model of the protein. If the superfamily is not known, sequence analysis or structural similarity searched can be performed to identify related proteins for use as templates in homology modeling studies. *Ab initio* loop prediction or *ab initio* secondary structure generation techniques are then used to complete the model (as shown in Figures 1-3). The structural variant model can be energetically refined by performing molecular mechanics calculations, for example, using an ECEPP type force field or through molecular dynamics simulations, for example, using a modified AMBER type force field. If necessary, the structures can be dynamically refined, for example, by using a simulated annealing protocol (e.g., 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection). For quality control, the protein structural characteristics, for example, stereochemistry e.g., phi/psi and side chain angles), energetics (e.g., strain energy), packing profile (e.g., packing factor per residue) and hydrophobic packing are evaluated and required to meet acceptable criteria before the structures are used in further studies or input into a structural polymorphism database.

Therefore, as taught in the specification, the step of "generating 3-D protein structural variant model from the sequences" in claim 23 can be done by a variety of methods including experimental methods (e.g., x-ray crystallography and NMR), from a protein structure database (e.g.the PDB), homology modeling, *de novo* protein folding algorithms and methodologies, other *ab initio* methods, and other computational protein structure prediction methods.

3. Presence of working examples

The specification provides working examples of generating 3-D structural variant models. In Example 1, 3-D models of mutant forms of HCV protease with different inhibitors are generated and used to assess binding correlations between experimental results and computational results. In particular, binding correlations of NS3/NS4A-peptide complexes were studied and used to validate the 3-D models of the NS3/NS4A-peptide complexes.

NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome and is involved in HCV replication. NS3 protease is considered a member of the chymotrypsin family and is a serine protease that is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions responsible for generating four viral proteins during viral replication. NS3 protease is inhibited by N-terminal cleavage products of substrate peptides. NS3 is thus a target for the design of antiviral drugs.

Active NS3 forms a heterodimer with a polypeptide cofactor NS4A. The crystal structure of NS3 with and without the NS4A cofactor is known in the art. Example 1 desribes binding studies of NS3/NS4A complexes with two peptide inhibitors. The binding studies were conducted *in silico* and compared to the experimental results of Ingallinella *et al.* ((1998) *Biochemistry 37*:8906-891.

Generation of 3-D structure of NS3/NS4A-peptide complex

The crystal structure of NS3/NS4A was regularized using molecular mechanics. Peptides were placed into the NS3 binding site by analogy with other serine proteases. The peptides studied were:

Sequence *	IC^{50}, nM	SEQ ID
Ac-Asp^1-D-Glu^2-Leu^3-Ile^4-Cha^5-Cys^6-COO-	15	1
Ac-Asp^1-L-Glu^2-Leu^3-Ile^4-Cha^5-Cys^6-COO-	60	2

* Cha = β-cyclohexylalanine

Monte Carlo (MC) simulations were performed on the NS3/NS4A-peptide complexes using ECEPP/3 forcefield. The sampling method was a biased probability Monte Carlo with random change of one variable at a time. A Metropolis acceptance criterion was applied after energy minimization (quasi-Newton, up to 1000 steps). Simulations were performed at a temperature of 1000° K. In the peptide, translation/rotation and all torsions were included in the simulation. Protein side-chain χ angles of residues that have at least one atom within 7.0 Å of any atom of the peptide were included. The energy function used in the MC simulations included ECEPP/3 terms for energy *in vacuo* (VDW, H-bond, electrostatic and torsion potentials); distance dependent electrostatics with e = 4.0; and surface energy with atomic solvation parameters. The total energies of the complexes were calculated including contributions from: ECEPP/3 VDW, H-bond, S-S bond and torsion terms; exact-boundary electrostatic energy with e = 8.0; and side-chain entropies. Hydrophobic free energies were estimated as sA, where A is accessible surface area and s is a tension constant of 0.03 kcal/molÅ^2.

The Monte Carlo (MC) simulations of the NS3/NS4A-peptide complexes were performed with multiple, relatively short MC runs (2000-5000 generated structures). New docking cycles were started from the lowest-energy or other interesting structures found in previous runs. Structures saved during various MC runs were sorted by total energies and RMSD, and compressed into a cumulative conformational stack.

Binding energies were calculated for representative structures of each complex thus obtained using the equation:

$$E_{bind} = E_o + E_{compl} - E_{pept} - E_{prot},$$

where E_{compl} is the energy of the NS3/NS4A-peptide complex, E_{pept} & E_{prot} are separate energies of the peptide and NS3/NS4A protein, respectively, and E_o is an adjustable constant.

The binding energy function included: exact-boundary electrostatic contributions; side-chain entropy; and surface tension hydrophobic terms. ECEPP/3 hydrogen-bonding terms were included with a weight of 0.5.

RMSD between pharmacophore atoms of peptides 1 and 2 were calculated for all pairs of MC structures. NS3/NS4A-peptide models were selected based on RMSD (e.g. RMSD $\leq$ 2.0 Å) and ΔE_{bind} (e.g. $\Delta E_{bind} < 5.0$ kcal/mol) for characterization and validation.

In the model validation studies, modifications were made to the NS3/NS4A-peptide complex models, and the binding energies of the modified complexes were correlated with those expected from experimental IC_{50} values. Changes in calculated binding energies upon modifications, ΔE_{bind} (calc), were compared to the values expected from ratios of inhibitory potencies, ΔE_{bind}(exp).

$$\Delta E_{bind}(exp) = RT\, ln(IC_{50}^{mod}/IC_{50}^{o}),$$

where IC_{50}^{o} and IC_{50}^{mod} are inhibitory potencies of the parent and modified compounds.

The correlation between experimental and calculated changes in binding energy upon ligand modifications in the binding site of NS3 is shown in **FIG. 4**.

The models were in agreement with SAR data for peptide inhibitors of NS3. Predicted changes in binding energy upon modification of the protein and peptides correlate reasonably well with the changes expected from IC^{50} ratios. For exmaple, standard deviations of ΔE_{bind}(calc) - ΔE_{bind}(exp) were 0.8 and 1.6 kcal/mol for Models 1 and 2, respectively, with correlation coefficients of 0.62.

After the largest outlier was removed from each dataset, correlations improved to 0.81 and 0.76, respectively.

Thus, the fact that the *in silico* studies correlated well with experimental data validates models for use in structure-based drug design methods and for other methods claimed in the instant application. Moreover, the correlation of the computational data with experimental data demontrates that the skilled artisan can use the protocols taught in Exmaple 1 to generate 3-D structural variant models.

4. Nature of the claimed subject matter

The claimed subject matter is directed to the prediction of clinical responses of patients by comparing 3-D protein structures of structural variants encoded by genes exhibiting polymorphisms to relational databases of 3-D protein structural variant models. Clinical data associated with structural variant models that are similar to the patients' structural variant models are used to predict clinical outcomes for the patient. As taught in the specification, clinical information that can be used to predict responses in patients includes, but is not limited to, patients receiving a specific treatment regimen or exhibiting a particular clinical response to a given drug, and the duration of a particular drug treatment (page 5, lines 1-4). Moreover, the protein structural variant models that are used in the comparison of patient data can be generated by experimental methods (e.g. x-ray crystallography or NMR), from a protein structure database, (e.g. PDB), homology modeling, *de novo* protein folding algorithms, other *ab initio* methods, computational protein structure prediction methods, and combinations thereof. As disclosed in the instant specification and as discussed below, these methods of generating protein structures are well known in the art.

5. Level of skill

The level of skill in this art of polypeptide structure and modeling is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat.

App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art. For example, Balaji disclose *ab initio* methods that can be used to generate polypeptide structures (U.S. Patent Nos. 5,331,573; 5,579,250; and 5,612,895). Dudek *et al.* discloses *ab initio* loop predictions and molecular modeling that can be used to generate polypeptide structures (J. Comp. Chem. (1998) 19:548-573). Balasubramanian discloses Ramachandran plots that can be used to generate polypeptide structures (Nature (1974) 266:856-857). Weiner and Ramnarayan disclose molecular modeling that can be used to generate polypeptide structures (J. Comp. Chem. (1986) 7:230-252; J. Chem. Phys. (1990) 92:7057-7076). Nanni *et al.* and Kroeger *et al.* disclose 3-D protein structures of HIV reverse transcriptase and protease (*Perspectives in Drug Discovery and Design 1*:129-150 (1993); *Protein Eng. 10*:1379-1383 (1997)). Love *et al.* and Yan *et al.* disclose the crystal structure of NS3 protein without the NS4A cofactor (*Cell 87*:331-342 (1996) and *Protein Sci. 7*:837-847 (1998)). Since the level of skill in the art is high, the specification does not require a high level of teaching in order to enable one of skill in the art to generate 3-D protein structures from sequence data.

6. State of the prior art:

At the time of the effective filing date of this application and before, the skilled artisan knew various methods of generating 3-D structures of proteins from sequence data. Further, there is a large body of literature directed to generating 3-D structures of proteins from experimental and computer-based methods.

The articles cited in the specification, of record in this application, describe various methods of generating 3-D protein structures. The following represents some exemplary articles that evidence the knowledge of those of skill in the art at the time of filing of the instant application:

Balaji *et al.*, "Method of Rational Drug Design Based on Ab Initio Computer Simulation of Conformational Features of Peptides," U.S. Patent No. 5,612, 895 (March 18, 1997), which describes *ab initio* prediction of the tertiary structure of polypeptides without any presumption as to the conformation of the underlying primary or secondary structure. The Balaji method involves computer simulation of polypeptides by simulating a real-size primary structure in an aqueous environment, shrinking the size of the polypeptide isobarically and isothermally, and expanding the simulated polypeptide to its real size in selected time periods. "Balaji plots" are used to identify those portions of the predicted peptide structure that are most flexible or rigid. The Balaji methods are used to generate polypeptide models that are used to design bioactive drug analogs (See U.S. Patent No. 5,736,509 (April 7, 1998); See also Balaji *et al.* U.S. Patent No. 5,331,573 (July 19, 1994) and U.S. Patent No. 5,579,250 (November 6, 1994));

Osguthorpe, "Improved Ab Initio Predictions with a Simplified, Flexible Geometry Model," Proteins: Structure, Function, and Genetics Suppl 3 (November 8, 1999) 186-193, which describes the *ab initio* prediction of the tertiary structure of T56, (a target that was predicted at the CASP3 meeting described by Sternberg *et al.* and Koehl *et al.*) and which demonstrates that for new folds, *ab initio* methods are as good as other methods in getting an approximation to the native structure;

Westhead and Thornton "Protein structure prediction," Curr Opin in Biotechnology (1998) 9:383-389, which describes improvements in comparative modeling studies;

Eisenhaber *et al.* "Protein structure prediction: recognition of primary, secondary, and tertiary structural features from amino acid sequence," Critical Rev. in Biochem and Mol. Biol. (1995) 30:1-94, which describes prediction of protein structure from amino acid sequence computational methods, threading methods, sequence alignment methods, and homology modeling;

Jones, "Successful *ab initio* prediction of the tertiary structure of NK-Lysin using multiple sequences and recognized supersecondary structural motifs," Proteins: Structure, function, and Genetics, Suppl 1 (1997) 185-191, which describes tertiary protein structure prediction based on the assembly of recognized structural fragments taken from highly resolved protein structures;

Samudrala *et al.*, "Ab initio protein structure prediction using a combined hierarchical approach," Proteins: Structure, function, and Genetics Suppl 3 (November 8, 1999) 194-198, which describes the prediction of 3-D structures for 13 proteins using lattice based scoring function in conjunction with distance geometry methods;

Dunbrack *et al.* "Meeting review: the Second Meeting on the Critical Assessment of Techniques for Protein Structure Prediction (CASP2), Asilomar, California, December 13-16, 1996," Folding and Design (1997) R27-R42, which reviews the comparative modelling, fold recognition, and *ab initio* structure prediction presented at CASP2; and

de Dios *et al.* "Secondary and Tertiary Structural Effects on Protein NMR Chemical Shifts: An ab Initio Approach," Science (1993) 260:1491-1496, which describes the use of NMR to refine protein structures;

These articles and patents are representative of the numerous ways to generate 3-D protein structures from sequence data. The articles range from pure experimental methods (such as NMR spectroscopy) to pure computational methods (such as *ab initio* methods). Therefore, the knowledge of those of skill in the art is extensive and methods for generating 3-D protein structures from sequences is well known.

7. Predictability

As is known to those of skill in the art (described above), the level of knowledge and skill in the generation of 3-D protein structures is so high that as of the effective filing date of the instant application, it would not have required

undue experimentation by one of skill in the art to use sequence data to generate 3-D protein structures. As noted above, one of skill in the art can use experimental methods (e.g. NMR and x-ray crystallography), computational methods, homology modeling, de novo prediction, *ab initio* methods, or any combination thereof to generate 3-D protein structures from protein sequences.

CONCLUSION

Thus, the specification of the instant application teaches a skilled artisan teaches a skilled artisan how to generate 3-D protein structures from sequence and how to make and use the elements of the claimed methods. In light of the breadth of the claims, the teachings, guidance, and working examples in the specification, the high level and extensive knowledge of skill of those in this art, it would not require undue experimentation for a person of skill in the art to generate 3-D protein structures from sequence data for use in the instant claims. As disclosed in the specification and in the cited art, the skilled artisan can use experimental methods, computational methods, homology modeling, and/or *ab initio* methods to generate 3-D protein structures even by using the protein sequence alone. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Rebuttal to comments by the Examiner

1. Rebuttal to Examiner's state of the art arguments

The Examiner alleges that the instant methods require *ab initio* methods to predict accurately the structure of a polymorphic peptide sequence in the absence of additional structure and that the best *ab initio* methods were unable to predict protein structure accurately in the absence of knowledge of structures of polypeptides with similarity to the polypeptide of interest as evidenced by Sternberg *et al.* (Curr Opin in Struc. Biol. (1999) 9:368-373) and Koehl *et al.* (Nature Struc. Biol. (1999) 6:108-111).

As noted above, claim 23 and claims dependent thereon are not limited solely to *ab initio* methods for generating 3-D protein structures from sequence

data. Experimental methods (e.g. NMR and x-ray crystallography), computational methods, homology modeling, de novo prediction, *ab initio* methods, or any combination thereof can be used to generate 3-D protein structures from sequence data. Even if *ab initio* methods were the sole methods of generating 3-D protein structures from sequence data, the Examiner's conclusion that *ab initio* methods are inadequate is incorrect.

The instant methods are directed to computer-based methods for predicting clinical responses in patients based on genetic polymorphisms. Models of structural variant proteins in patients are generated and compared to structural variant models in a database. Clinical data associated with structural variant models that are similar to the patient's structural variant models are used to predict clinical outcomes for the patient. Thus, the methods are directed to generating 3-D protein structures that can be **compared** to each other for the purpose of **determining the similarity between the 3-D protein structures**, not to generating 3-D protein structures that are accurate. Therefore, the accuracy of the generated 3-D protein structures is irrelevant as long as comparison between the 3-D protein structures can be made.

Sternberg *et al.* and Koehl *et al.* are meeting review articles of the third comparative assessment of techniques of protein structure prediction (CASP3) held during 1998. The references describe three approaches to protein structure prediction, namely comparative modeling, fold recognition, and *ab initio* prediction.

The Examiner alleges that both of these references disclose that *ab initio* algorithms had relatively poor ability to predict structure and predicted the positions of only about half of the residues in the sequence in the absence of knowledge of the structures of other similar polypeptides (Sternberg *et al.* Figure 2 and Koehl *et al.* Table 1).

Figure 2 in Sternberg *et al.* shows the best predictions of protein targets in the fold recognition and *ab initio* sections. Contrary to the Examiner's

assertion that *ab initio* algorithms had relatively poor ability to predict structure, Sternberg *et al.* discloses that in the *ab initio* section, algorithms were available that generated 3-D protein from protein sequences without employing fold recognition good models for several targets (Sternberg *et al.* page 371, column 2, lines 31-34). Figure 2 also shows that for two targets, *ab initio* methods yielded better models than fold recognition methods that used a template fold that was a distant homologue (i.e. structurally similar) of the target peptide (Sternberg *et al.* page 371, column 1, lines 10-19). Thus, in some instances, the *ab initio* methods were able to predict structures better than methods that used knowledge of polypeptide similarity. Contrary to the Examiner's assertion, Sternberg *et al.* does not disclose that *ab initio* methods have a poor ability to predict protein structure.

Table 1 in Koehl *et al.* shows the best results of the structure prediction of CASP3 targets based on comparative modeling, fold recognition, and *ab initio* methods. Although some *ab initio* methods predicted the positions of only about half of the residues in the sequence, Koehl *et al.* does not disclose that *ab initio* algorithms have a poor ability to predict protein structure. In fact, Koehl *et al.* discloses that the quality of models for the five easiest *ab initio* targets were as good as that of the four most difficult folding recognition targets (Koehl *et al.* Table 1 and page 109, column 3, lines 52-56). For example, the prediction of target 56 as a new fold was close to the native structure of the target peptide with a Cα RMS of 6Å (Table 1). Additionally, Koehl *et al.* also discloses that although the CASP assesses the ability of the best practitioners in the field to predict protein structure, it does not test how well other scientist can expect to do, or how well totally automated methods will do in *ab initio* structure prediction (page 111, column 2, 5-10). Therefore, Koehl *et al.* does not disclose that *ab initio* methods have a poor ability to predict protein structure.

Further, as noted above, *ab initio* methods that can be used to generate 3-D protein structure from protein sequence data were available at the effective

time of filing of the instant application. For example, as disclosed in the specification, the Balaji *et al.* methods can be used to generate 3-D protein structures from sequence data without any regard to the conformation of the underlying primary or secondary structure. As noted above, the Balaji *et al.* methods generated 3-D polypeptides models of endothelin-1 that were good enough to design peptide analogs therefrom that mimic the surface features endothelin-1 and modulate the activity of endothelin-1. Since the Balaji methods generated polypeptide models that were good enough to design bioactive analogs, the Balaji methods are good enough to design polypeptide models that can be used in the computer-based methods of predicting clinical reponses described in the instant application.

Assuming arguendo that *ab initio* methods have a poor ability to predict protein structure without structural information on other structurally similar polypeptides, *ab initio* methods can be used to generate 3-D protein structures that can be used in the instant methods. As noted above, the instant methods are not directed to generating accurate 3-D protein structures but to generating 3-D protein structures that can be **compared** to each other for the purpose of **determining the similarity between 3-D protein structures** found in databases of structural variant models and in patients. Once 3-D structural variant models are determined to be similar to the structural variant model from patients, clinical data associated with those structural variant models that bear similarity to those of patients are used to predict clinical outcomes for patients. Therefore, the accuracy of *ab initio* methods in generating 3-D protein structures is irrelevant.

2. Rebuttal to the Examiner's predictability arguments

The Examiner alleges that Sternberg *et al.* and Koehl *et al.* show that *ab initio* methods of structure prediction from polypeptide sequence information alone is not predicted to result in an accurate structure of a complete polypeptide.

As noted above, Sternberg *et al.* discloses that *ab initio* methods generated good 3-D protein models from protein sequences alone without employing fold recognition and that, in some instances, *ab initio* methods were able to predict structures better than methods that used knowledge of polypeptide similarity. (Sternberg *et al.* page 371, column 1, lines 10-19, and column 2, lines 31-34). Sternberg *et al.* does not disclose that *ab initio* methods have a poor ability to predict protein structure from protein sequences alone.

As also noted above, Koehl *et al.* does not disclose that *ab initio* algorithms have a poor ability to predict protein structure despite the fact that some *ab initio* methods predicted the positions of only about half of the residues in the sequence. In fact, Koehl *et al.* does not disclose that in general *ab initio* methods are inaccurate in predicting protein structure based on sequence alone because the reference discloses that the CASP does not test how well other scientists can expect to do or how well totally automated methods will do in *ab initio* structure prediction (page 111, column 2, 5-10). As noted above, Koehl *et al.* does not disclose that *ab initio* methods have a poor ability to predict protein structure.

Assuming arguendo that *ab initio* methods are inaccurate in predicting protein structure based on sequence alone, accuracy is irrelevant to the instant claimed methods. As noted above, the instant methods are not directed to generating accurate 3-D protein structures but to generating 3-D protein structures that can be **compared** to each other for the purpose of **determining the similarity between 3-D protein structures** found in databases of structural variant models and in patients. Once 3-D structural variant models are determined to be similar to the structural variant model from patients, clinical data associated with those structural variant models that bear similarity to those of patients are used to predict clinical outcomes for patients. Therefore, the accuracy of *ab initio* methods in generating 3-D protein structures is irrelevant.

THE REJECTION OF CLAIM 23 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the claim language is indefinite. The bases for this rejection are discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

There are no requirements for terms to be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, an applicant is entitled to be its own lexicographer [see, *e.g.*, MPEP 2111.01 "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage and utilize terms within the claims that are clear from a reading of the specification. *In re Hill*, 73 USPQ 482 (CCPA 1947)."]. When applicant has provided definitions in the specification, the claims are interpreted in light of such definition.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass*

Corp. v. Libby-Owens Ford Col., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); See, also, *Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

Claim 23

Claim 23, as amended herein, and claims dependent thereon are described above.

1. Claim 23 is alleged to be indefinite in the recitation of the phrase "derived based on" in page 47, line 27, because it is allegedly not clear what the phrase means in relation to the rest of the claim. The inadvertently added verb "derived" is deleted from claim 23, thereby obviating this rejection.

2. Claim 23 is alleged to be indefinite in the recitation of the limitation "the structural variant-drug complex models" because there is allegedly insufficient antecedent basis for this limitation in the claim. As amended, the article "the" is deleted, thereby obviating this rejection.

3. Claim 23 is alleged to be indefinite in the recitation of the phrase "a molecular graphics interface for 3-D molecular structure visualization; functionality for protein sequence and structural analysis; database searching tools" because those recited elements cannot be a part of a database as

required by the claim. As amended, this language is deleted from claim 23, thereby obviating this rejection.

4. Claim 23 is alleged to be indefinite for the recitation of the phrase "based on" in page 48, line 9, because it allegedly is not clear as to what the phrase means in relation to the rest of the claim. As amended herein, the phrase "based on the same" is replaced by the phrase —encoded by the— to more particularly point out that the structural variant is the product of a gene exhibiting genetic polymorphisms.

5. Claim 23 is alleged to be indefinite in the recitation of "the same gene associated with a polymorphism in a patient," because there allegedly is insufficient antecedent basis for this limitation. As amended herein, replaces the phrase "the same gene associated with a polymorphism" is replaced with the phrase —the gene exhibiting genetic polymorphism— to reference the antecedent therefor.

6. Claim 23 is alleged to be indefinite in the recitation of the phrase "screening/comparing" becsause it is allegedly unclear if both or only one of the processes is part of the claim. Claim 23, as amended herein, replaces the phrase "screening/comparing" with the phrase —screening or comparing— for grammatical clarity, thereby obviating the rejection.

* * *

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman, Reg. No. 33,779

Attorney Docket No. 24737-1906B
Address all correspondence to:
Stephanie L. Seidman, Esq.
HELLER EHRMAN WHITE & McAULIFFE
4350 La Jolla Village Drive, 7th Floor
San Diego, California 92122-1246
Telephone: 858 450-8400
Facsimile: 858 587-5360
email:sseidman@HEWM.com